to determine the value of other preparations derived from immune serum aimed at conferring passive immunity.

3. Animal models which closely resemble human infection should be sought, in order to study the pathogenesis and immune mechanisms of pertussis. A mouse model of respiratory infection already exists and deserves further exploration.

4. Clinical trials should be conducted with other immunoglobulin preparations that may have better experimental evidence for efficacy. Such studies could be carried out where the incidence of pertussis in childhood is high, or in special situations such as outbreaks among adults.

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SPECIFIC PRODUCT REVIEWS

Pertussis Immune Globulin (Human) Manufactured by Cutter Laboratories, Inc.

1. *Description.* This product is a solution of immunoglobulin prepared from venous blood of humans hyperimmunized with pertussis vaccine. It contains 16.5 percent ± 1.5 percent protein dissolved in 0.3 M glycine and preserved with 1:10,000 thimerosal. The pH is adjusted withu sodium carbonate. Each 1¼ mL dose contains a quantity of immunoglobulin equivalent to approximately 25 mL of human hyperimmune plasma.

Fresh citrated plasma is collected by plasmapheresis and fractionated into components of plasma using the Cohn cold alcohol method. The pool of plasma is chosen on the basis of minimum pertussis titer and no regard is given to the number of donors. The final product solution is sterilized by filtration. Pertussis agglutination titers are determined but the standard used is not given. Donors, whose health status has been checked, receive a basic series of three injections of Eli Lilly and Company's pertussis vaccine during a 12-month period and a fourth injection during a second 12-month period. A donor consent form is supplied.

2. *Labeling*—a. *Recommended use/indications.* The product is said to be indicated in the prophylaxis and treatment of pertussis. The dose is 1¼ mL given as soon after exposure as possible, and in therapy it is recommended that the same dose is repeated after 24 or 48 hours, sometimes again after 1 to 2 weeks. The product is given intramuscularly only, and not intravenously.

b. *Contraindications.* The product is contraindicated in individuals who are known to have an allergic response to immunoglobulin. There is a warning against intravenous use. Slight soreness may occur at the injection site; sensitizations is extremely rare but may occur. There have been a few instances of angioneurotic edema, nephrotic syndrome, and anaphylactic shock after injection.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* Several studies with pertussis immune globulin are cited in the submission to the Panel (Ref. 1), seven of these utilized the product of this manufacturer. Whereas uncontrolled studies generally reported favorable results, the controlled studies failed to show any significant differences between control and treatment groups. The efficacy of the product, not only in treatment but also in prophylaxis, appears in doubt.

The only somewhat controlled study which reported favorable results is the one by Hatz (Ref. 2) who studied streptomycin with and without hyperimmune serum in treatment of pertussis. However, the conclusions appear not be to statistically validated.

It is disconcerting that controlled studies, generally carried out after 1950 when pertussis had become a relatively mild disease and effective antibiotics were available, all report a lack of statistically significant benefit from pertussis immune globulin. On the other hand, uncontrolled or poorly controlled studies carried out with whole immune serum in the 1930's and 1940's suggested great benefit, especially in prophylaxis. If the protective antibody is found in the IgM fraction of the immune globulin as suggested in "Infectious Diseases" by Krugman and Ward (Ref. 3), how can the IgG (which is the principal content of hyperimmune globulin) be of any help? Maternally acquired immunoglobulin is known not to be protective.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several clinical trials report no adverse effects. Rate instances of angioneurotic edema, nephrotic syndrome, and anaphylactic shock are listed as possible adverse reactions. No data from the complaint file are submitted

c. *Benefit/risk ratio.* The benefits of this product both in prophylaxis and treatment are in doubt, although there is little risk (isoimmunization, allergic reactions).

4. *Critique.* This is a well-documented submission except that data from the manufacturer's complaint file were not submitted. It is unclear how many donors make up the pool for pertussis immune globulin (the Bureau of Biologics requires a minimum of 10 individuals). The label states that the donors are given Cutter Laboratories' pertussis vaccine, other sections of the manufacturer's submission indicate that Eli Lilly's vaccine is used. Information on adverse reactions to repeated administration of pertussis vaccine in adults and the procedure utilized in the production of pertussis immune globulin (human) should be developed. This

information should include data on the type of vaccine used. The agglutination test, including standards, is not described. The submission contains a thorough listing of human studies of pertussis immune globulin, including several of the manufacturer's own product. Their own interpretation of these studies is that the product is efficacious. It is unfortunate that this conclusion is based on uncontrolled studies, and not on the controlled ones, which do not prove any statistically significant benefits.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product.

Pertussis Immune Globulin (Human) Manufactured by Travenol Laboratories, Inc., Hyland Division

1. *Description.* This product is a 16.5 (± 1.5) percent solution of the immunoglobulin fraction (Cohn Fraction II) of the serum of healthy adults hyperimmunized with pertussis vaccine. The solution is made isotonic and stabilized with 0.3 molar glycine. It contains 0.1 percent sodium chloride and 0.01 percent thimerosal as a preservative. Cryoprecipitate is removed by centrifugation and reserved for other use. Fraction II is obtained from Fraction I, II, III by the Cohn method with some modifications. Donors are given 3 doses (0.5 mL) of pertussis vaccine subcutaneously at weekly intervals, the fourth dose is given after 4 weeks, and later doses are given at 4-week intervals as long as the donor remains on the program. Plasmapheresis is performed twice weekly.

The product is available in 1.5 mL single dose vials.

2. *Labeling*—a. *Recommened use/indications.* In *prophylaxis,* one 1.5 mL dose of pertussis immune globulin (human) is recommended for a child as soon after exposure as possible. A second dose, 1 week after the first, is desirable. If use of the globulin is delayed more than 1 week after exposure, larger doses should be given at 1 to 2 week intervals.

In treatment, for children already showing symptoms of pertussis, one 1.5 mL dose should be given as soon as possible, with additonal doses at 2-day intervals until recovery has begun. For critically ill children, the initial dose might well be doubled. In cases of pertussis pneumonitis, the globulin treatment may be supplemented with suitable sulfonamide or antibiotic therapy.

It is clearly stated that the product should be given intramuscularly and not intravenously.

b. *Contraindications.* None are listed. Under reactions the remote possibility of serum sickness and anaphylaxis are mentioned, as well as local tenderness and stiffness. A warning againts intravenous infection is given.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* The manfacturer's submission to the Panel (Ref. 4) cites the literature of pertussis immune globulin, but they appear not to have conducted any field tests of their own product. The product is tested for potency by measurement of agglutination titers. The aggflutination titers of the lot under test, a house reference lot, and the starting plasma pool are determined, using as the antigen a commercially available licensed pertussis vaccine, always from the same manufacturer. The lot under test must show at least 16 times concentration of antibody over the starting plasma pool (i.e., 4 doubling dilutions difference) and the house reference lot must show the same titer as it showed in previous tests, plus or minus 1 doubling dilution. No refereence or standard from the Bureau of Biologics is being utilized.

b. *Safety.* This product is tested for purity, residual moisture, pyrogens, electrophoretic purity, "general safety," and stability.

(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data on human safety for this specific product were supplied other than from the general literature. No data from the manufacturer's complaint file were submitted.

c. *Benefit/risk ratio.* The benefits of this product both for use in prophylaxis and treatment are questionable. Serveral uncontrolled studies report beneficial results, but the controlled studies, even those investigating the prophylactic use (Morris (Ref. 5) and Place (Ref. 6)) report no significant differences between patients given pertussis immune globulin and other material. The risks are minimal, but allergic reactions and isoimmunization have to be considered.

4. *Critique.* The most difficult problem is to determine if the current literature supports the belief that the use of pertussis immune globulin is effective in prophylaxis, let alone treatment of pertussis. The manufacturer's own product has not been field tested; however, such a test would be very difficult to institute. Data from complaint files are lacking. The Bureau of Biologics does provide a U.S. standard antipertussis serum, and the provisional requirements state that each lot of pertussis immune globulin shall contain a pertussis antibody level of not less than 500 pertussis units per vial compared with this standard. Information on adverse reactions to repeated administration of pertussis vaccine in adults, a procedure utilized in the production of pertussis immune globuline (human), should be developed. This information should include data on the types of vaccine used. Because sulfonamides are not the first choice in treatment of pertussis, the advice regarding supplementary treatment should be reworded: substitute "sulfonamide or antibiotic therapy" with "antimicrobial therapy."

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product.

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Generic Statement on Tetanus Antitoxins

Tetanus is an acute disease of the nervous system caused by infection with the tetanus bacillus, *Clostridium tetani,* which produces an extremely potent neurotoxin that is lethal to man in miniscule amounts (approximately 7 millionths of a milligram). The tetanus bacillus also produces lesser reactive substances. The disease is of major importance, killing perhaps 1 million people worldwide annually. The tetanus bacillus is probably primarily a resident of the intestinal tract of various animals, but spores are widely distributed in soil and dirt, and when carried into devitalized injured human tissues that is low in oxygen, the spore form of the bacillus can germinate, liberate toxin, and hence cause the disease. The disease can be prevented by

immunization with tetanus toxoid. Immunization is indicated for everyone, since natural immunity, if it exists at all, is exceedingly rare in man; not even the disease itself produces immunity in those who recover from it.

In the 1890's, tetanus antitoxin was developed, primarily in horses, by hyperimmunization—first by injection of slowly increasing amounts of tetanus toxin, and later, when it became available, by sequential injections of tetanus toxoid. The serum from such animals contained varying amounts of antibody capable of neutralizing tetanus toxin in experimental animals; therefore it has been used on a worldwide basis ever since both for the prophylaxis of tetanus in unimmunized persons thought to be exposed to the disease, and for treatment of the disease.

Both the safety and efficacy of tetanus antitoxin of animal origin have been the subject of concern and disagreement ever since its introduction, because of the frequency of reactions—not infrequently severe and sometimes fatal—following the injection of horse serum in sensitive individuals, and because unequivocal data regarding its efficacy have never become available. Substitution of antiserum prepared in cattle or sheep did not solve either problem, and during the past 15 years attention has been turned to the preparation of concentrated antitetanus antibody solutions from immunized or hyperimmunized human donors. The human preparation, disignated tetanus immune globulin, has eliminated the problem of reactions to heterologous serum, but the problem of efficacy remains unsettled. Nevertheless, the theoretical considerations and the clinical impression that either or both of these products are of value have led to their very general use, for prophylaxis of tetanus in previously unimmunized persons incurring a risk of contracting tetanus, and in the treatment of clinical tetanus.

Nature of Product

Tetanus antitoxin consists of the partially purified globulin fraction from the serum of animals (generally horses) hyperimmunized with multiple sequential doses of tetanus toxoid and sometimes toxin as well. Potency in units is determined by reference to the U.S. standard antitoxin. Antitoxin of bovine or ovine origin is similar except for minor differences in the prodominant type of antitoxin-containing globulin.

Tetanus immune globulin is the gamma globulin fraction from a pool of human donors who have either been selected because they already posses a sufficiently high serum antitoxin level against tetanus toxin, or else have been hyperimmunized so that their serum antitoxin level is suitably high.

Production

For the production of tetanus antitoxin, the best responders are selected from a number of horses that have been given several properly spaced injections of tetanus toxoid and further immunized until test bleeding showed that their serum antitoxin level is high enough to yield a concentrated antitoxin of acceptably high titer, e.g., 1,500 units or more per mL. Present day harvesting of serum is done by plasmapheresis, collecting 8 to 9 liters of blood and retransfusing the separated cells, on a regular schedule such as every 2 weeks. The plasma is fractionated, unsually by precipitation of the antitoxic antibodies with ammonium or sodium sulfate, yielding a mixture of proteins that contains a high proportion of the antitoxic globulin which is, in the horse, largely a beta-globulin. The precipitate is reconsitituted, dialyzed, and ajusted to yield approximately a 20-percent concentration of serum proteins. Further purification of the original serum is usually carried out under specified conditions of pepsin digestion, which hydrolyses much of the nonglobin protein present, yielding a preparation with fewer nonspecific proteins and a higher ratio of beta-globulin, modified by digestion but still fully against toxin. In practice, the proportion of specific antitoxin in the usual product is probably about 1 or 2 percent.

The digested, fractionated, dialysed product is adjusted to a concentration suitable for filling (either as prophylactic doses of 1,500 units or therapeutic doses commonly furnished as 10,000 units per vial). It is then tested for identity, safety, and for potency in units per mL by mixture with toxin in graded dilutions and injection of each mixture into groups of guinea pigs. A preservative (usually thimerosal) is added, and the product is filled with a 20 percent excess or more, according to Federal regulations.

Tetanus immune globulin. Production from normal donors is based on availability of outdated blood from cooperating blood banks and selection of those with high tetanus antitoxin titers, commonly selecting those that show eight units or more by hemagglutination. Alternatively, selected hyperimmunized donors may be bled by plasmapheresis, yielding a human serum pool of higher titer than is obtainable from selected normal adult blood. In either case, the plasmas of at least 10 donors are pooled, and the pool is fractionated according to the alcohol method of Cohen et al., yielding a preparation with over 90 percent gammaglobulin and conforming to the limitations set by Federal regulations regarding the presence of other globulins. The immune globulin is stabilized with 0.3 M glycine, titrated for tetanus antitoxin content as with animal serums, and diluted before filling to contain approximately 16.5 percent globulin. A preservative (normally thimerosal 0.01 percent) is added. The usual preparation is distributed in 250-unit amounts (plus the standard excess required by regulations) in a volume normally ranging from 2 to 4 mL.

Use and Contraindications

Tetanus antitoxin, like tetanus immune globulin, may be used for the prevention of tetanus following tetanus-prone injuries in unimmunized individuals or those whose immunization status is uncertain or for the treatment of clinical tetanus. For prophylaxis of injuries, tetanus antitoxin is generally considered to be indicated, if tetanus immune globulin is unavailable, in individuals having suffered injuries, burns, etc., judged by the physician as potentially at risk of developing tetanus. Prior to the injection of this material, the patient must be carefully questioned regarding any history suggesting sensitivity to horses or horse serum and should be tested for such sensitivity by conjunctival (1:10 dilution) or intradermal (1:100 dilution) test with the serum for freedom from reactions. Some experts advocate instead a "tolerance test" with 0.1 mL of a 1:100 dilution given subcutaneously. No test system is totally reliable and the patient must be watched for at least 1 hour after the antitoxin has been injected. The minimum dose is 1,500 units, but most authorities agree that this is insufficient and recommend a minimum of 3,000 units; some give 10,000 units routinely. If the wound is more than 24 hours old, some clinicians recommend doubling the dose. Epinephrine must be at hand at all times during testing and injection.

Special attention is required for babies born to unimmunized mothers under conditions conducive to neonatal tetanus. Such babies should be injected with 1,500 units of tetanus antitoxin or, if it is available, 500 units of tetanus immune globulin (see below). Sometimes the mother is also at risk, in which case she should be given prophylaxis as outlined for any patient at risk of developing tetanus.

Tetanus antitoxin is contraindicated in individuals with a history of sensitivity to horses, horse dander, or

horse serum, and should be given with extreme caution to anyone who has previously received any injections containing horse serum. In the presence of clearcut evidence of hypersensitivity, tetanus immune globulin should be used for prophylaxis even if its procurement means a delay of 24 hours. Although some believe that antibiotics are of value in the prophylaxis of tetanus, the available data do not support this belief. Nevertheless, antibiotics represent the only alternative when antitoxin-containing preparations are unavailable.

Prophylaxis with tetanus immune globulin is carried out without previous testing for sensitivity, but epinephrine should be at hand. The indications are the same as with antitoxin, but the dose is ⅓ to ⅙ the dose with equine antitoxin (250 to 500 units) since tetanus immune globulin is homologous and the half-life in vivo is about 3 weeks.

For therapy of tetanus, some clinicians prefer equine tetanus antitoxin because unlike tetanus immune globulin it can, with caution, be given intravenously and because 80 years of clinical experience has indicated that it may be of value. There is no general agreement as to the dose required for effective therapy, because it is quite evident that recovery from tetanus depends on many factors (sedation, debridement, prevention of spasms, prevention of infection, maintenance of respiration, etc.). Theoretical considerations and certain studies support the view that little is gained by giving more than 5,000 to 10,000 units of antitoxin. Others advocate much larger doses. It is established that the only function of antitoxin is to neutralize freshly liberated toxin from the infected source, i.e., antitoxin does not neutralize toxin already fixed to tissues. It is customary to give ½ the selected dose intravenously, the other half intramuscularly, after following the test precautions outlined above for the use of the product in prophylaxis. An additional precaution is to give 0.1 mL intravenously and wait ½ hour. If this small dose is tolerated, the patient will generally tolerate the remainder, which should nevertheless be given extremely slowly since some patients react at higher thresholds than others.

There is no general agreement on the value of continued therapy with antitoxin after the initial dose. By 7 to 10 days after the first dose, the majority of patients are sensitized to the horse serum and rapidly eliminate the antiserum.

Therapy with tetanus immune globulin has not been practiced for about 15 years. With generally available preparations of tetanus immune globulin the product must be given intramuscularly (NOT intravenously) which delays absorption so that the peak titer of antitoxin in the patient's serum will not be reached for 2 to 3 days. However, some clinicians have found that tetanus immune globulin can be given very slowly by intravenous drip without untoward reactions. This practice requires further study before endorsement. No firm guidelines regarding dosage exist, a commonly selected dose being 3,000 units. On the other hand, experimental animal studies suggest that the therapeutic dose of antitoxin is the same whether the serum is homologous or heterologous in origin; on this basis, at least 5,000 to 10,000 units of tetanus immune globulin should be given.

Preliminary sensitivity tests are not needed prior to injection of tetanus immune globulin; however, since patients will on rare occasions be sensitive to the preservative, to a specific allotype of globulin in the preparation, etc., therefore epinephrine should be at hand when this product is given.

Safety

Like other animal sera, equine tetanus antitoxin can cause serious or fatal anaphylactic reactions in a small proportion of people and the discomfort of serum sickness in a much larger proportion of people. Therefore, its use always incurs at least a small risk. Parallel experience with prophylactic diphtheria antitoxin has disclosed about 1 death per 50,000 persons injected.

Being homologous in origin, tetanus immune globulin is almost reaction-free if given intramuscularly. However, it can cause alarming hypotensive reactions if given intravenously.

Efficacy

The use of tetanus antitoxin or tetanus immune globulin for the prophylaxis of tetanus is endorsed by most physicians on the basis of logic and clinical experience, although unequivocal proof of efficacy is not available. Both preparations can protect animals under experimental conditions against either toxin or spore challenges. Data from World War I suggested, but did not prove, that antitoxin prophylaxis was of significant value. On the other hand, 1 reviewer has collected reports of 5,000 failures of tetanus antitoxin to prevent tetanus and failures of prophylaxis have occurred with tetanus immune globulin as well. Such data do not prove that the product is ineffective, but they clearly show that there are limitations to its value. These may be due to inability to prevent fulminating tetanus, delay in prophylaxis, failure to prevent delayed tetanus, rapid metabolism of the antitoxin, and various other causes.

With regard to therepy, many reports have given conflicting results, but most reliable studies have tended to suggest that moderate doses of antitoxin are of some value, the optimal dose probably ranging between 10,000 and 20,000 units. However, as noted above, the role of antitoxin in the treatment of tetanus may be secondary to the crucial importance of sedation, maintenance of respiration, and control of infection. Likewise, deaths from tetanus have occurred following the therapeutic use of tetanus immune globulin. Except for its freedom from the danger of reactions and from rapid elimination from the circulation of the host, tetanus immune globulin is subject to the same limitations as tetanus antitoxins: it cannot reverse the effects of toxin already fixed to tissue, and the clinical management of tetanus is the same (except for serum reactions) with either agent. Clinicians will continue to use these products for treatment until they are fully evaluated despite incomplete evidence as to the efficacy of either agent for the treatment of tetanus.

The Panel believes that tetanus immune globulin and tetanus antitoxin (as an alternative) should be classified as Category I for prophylactic purposes. Although unequivocal proof of effectiveness for this purpose is not available, theoretical considerations and uncontrolled clinical experience support an assessment of probable effectiveness. Furthermore, it is unrealistic to expect that a study could be defended that would withhold tetanus immune globulin (or tetanus antitoxin) from a patient for whom it would be indicated under the Public Health Service Advisory Committee on Immunization Practices guidelines on wound management.

On the other hand, the therapeutic use of tetanus immune globulin and/or tetanus antitoxin is a somewhat different matter for the reasons discussed above. There is far less of a consensus among clinicians concerning the therapeutic effectiveness of these products in cases of tetanus. The number of years required to obtain additional data are indeterminate and the possiblity of controlled trials is very small because of the relatively low incidence of the disease and the probable low effect of the antitoxin. Although a Category IIIA was considered, the number of years required to obtain additional data are

indeterminant, and the possibility of controlled trials is very small. For this reason, a Category I classification for therapeutic use of tetanus immune globulin and/or tetanus antitoxin is recommended.

Special Problems

In the United States, tetanus immune globulin has virtually superseded equine antitoxin for prophylactic use, but the equine product is still used in therapy, presumably because of its acceptability for intravenous administration and possibly because of cost and availability. Clearly, if the problem of intravenous use of tetanus immune globulin could be surmounted, there would be little reason for maintaining supplies of equine antitoxin. Furthermore, a number of preparations of tetanus immune globulin have been made experimentally, either in the United States or Europe, which appear suitable for intravenous use. Therefore, it appears that the problem of developing a satisfactory intravenous tetanus immune globulin product may be soluble.

Further evidence for the prophylactic and therapeutic efficacy of tetanus immune globulin is needed, but for ethical reasons a controlled study in the United States cannot be easily done. However, one comparison between tetanus immune globulin and equine antitoxin (in neonatal tetanus) has already been conducted, and no difference was noted. As indicated earlier, such a result is inconclusive as to the effectiveness of either agent inasmuch as untreated controls were not included.

Recently the old but discarded practice of intrathecal administration of equine antitoxin has been revived and is under systematic study overseas, using preparations free of the irritating preservatives that in the past apparently caused severe reactions. Such studies should be watched with interest since they might have application to the similar use of appropriately modified tetanus immune globulin.

It should be noted that none of the above problems would exist if active immunization were universal.

Recommendations

1. Universal active immunization against tetanus should be promoted.

2. Support any studies necessary to establish the availability, safety, stability, and potency of tetanus immune globulin suitable for intravenous use.

3. Support studies, clinical or in animals, to provide further information of value in judging the value of tetanus immune globulin in prophylaxis and therapy of tetanus.

4. Review and follow the accumulating data on intrathecal therapy with a view to its possible applicability to treatment of human tetanus with tetanus immune globulin.

5. Further information should be obtained regarding the possibility of a significant reduction in the reactivity of animal serum.

Basis for Classification

In the absence of controlled studies, difficult to obtain with this now rare (in the United States) life-threatening disease, the Panel could not insist on such evidence of efficacy. There is a sufficient body of historical data suggesting that tetanus antitoxin is of some effect, albeit marginal, in the treatment and prophylaxis of tetanus to justify classification in Category I.

Bibliography

See Bibliography for tetanus toxoid.

SPECIFIC PRODUCT REVIEWS

Tetanus Antitoxin Manufactured by Istituto Sieroterapico Vaccinogeno Toscano Sclavo

1. *Description.* This antitoxin is a sterile aqueous solution of enzyme-refined and concentrated immunoglobulins obtained from the plasma of horses hyperimmunized with tetanus toxin and/or toxoid. The plasma is pepsin-digested and precipitated in ammonium sulfate. The precipitate is collected, dialyzed, made up to 0.85 percent sodium chloride and 0.3 percent metacresol at pH 6.4, and filtered for bulk chilled storage. It is tested for titer, pyrogens, pH, electrophoretic composition, protein concentration, preservative concentration, and sterility. These tests, plus tests for identity, potency, stability, and total solids, are done for each filling which may be in vials holding 1,500, 3,000, 5,000, or 25,000 units (plus excess for dating as may be required).

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for prevention and treatment of tetanus when tetanus immune globulin is not available. Prevention is indicated for individuals who have had two or fewer doses of tetanus toxoid and who have tetanus-prone injuries that are more than 24 hours old. Tetanus toxoid (plain or adsorbed) should be given in a different syringe at a different site, and the immunization completed later as per schedule.

Precautions include careful inquiries regarding allergies of any type and previous injections of serums. Skin tests (1:1,000, 0.1 mL intradermally) and eye tests (1 drop of 1:10 dilution into conjunctiva) are mandatory. Normal saline controls should be used. Interpretation of skin test results is described. Epinephrine 1:1,000 should be at hand in a syringe. In the event of a positive sensitivity test, a so-called "desensitization" sequence of injections is described.

Adverse reactions of the various types included under "serum sickness" are said to occur in about 10 percent of patients, more frequently with large doses. The usual dose is 1,500 to 5,000 units for prophylaxis, 50,000 to 100,000 for treatment.

b. *Contraindications.* Intravenous injections in patients showing positive sensitivity tests.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission to the Panel (Ref. 1) states that "The efficacy of the product has been confirmed by the good results obtained through the years in Italy and abroad" and cites 8 references including the American Academy of Pediatrics "Red Book"—but not Bianchi (Ref. 2) (who has collected reports of 5,000 prophylactic failures).

b. *Safety*—(1) *Animal.* Two thousand lots have been tested in guinea pigs and/or mice, with no unsatisfactory results. This product meets Federal requirements.

(2) *Human.* A few million vials have been marketed in the last 5 years without any "significant complaints" according to data submission.

c. *Benefit/risk ratio.* In the absence of tetanus immune globulin, the available evidence indicates that the benefit-to-risk assessment for this product would be satisfactory for the recommended uses.

4. *Critique.* This is a standard enzyme-purified antitoxin which appears to be prepared and tested with all necessary precautions and should be as safe and effective as any licensed tetanus antitoxins. The label does not explain the exclusion of this product from use in fresh wounds in the unimmunized.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Tetanus Antitoxin Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for this product for which they were licensed at the time this